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Clinical Characteristics and Genetic Analysis of MYH7-Related Pediatric Cardiomyopathy—A Multicenter Cohort Study

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Abstract

Objective

The clinical phenotypes of MYH7-related pediatric cardiomyopathy are diverse.This study aims to analyze the clinical characteristics, prognosis, and domain-associated genetic characteristics of MYH7-related pediatric cardiomyopathy.

Methods

This was a multicenter retrospective cohort study. Children with MYH7 gene mutations who first or revisited ten domestic tertiary pediatric cardiovascular hospitals from January 2020 to December 2025 were enrolled. Based on the initial echocardiogram, the patients were divided into three groups: dilation phenotype group, hypertrophy phenotype group, noncompaction cardiomyopathy(NCM) phenotype group. General clinical data, laboratory test, echocardiogram and genetic

results

were collected from the medical record system. All children were followed up until December 2025, and follow-up echocardiogram

results

and occurrence of endpoint events were recorded. Log-rank test was used to assess differences in follow-up outcomes among groups. Spearman correlation analysis was used to examine the relationship between clinical phenotype and functional domain, and multiple logistic regression analysis was used to analyze the association between clinical phenotype and genetic functional domain.

Results

A total of 75 children with MYH7 gene mutations were enrolled, including four families. The median age at first diagnosis was 20.0 (3.0, 80.0) months, with 47 males (62.7%). Based on echocardiogram, there were 34 cases (45.3%) in dilation phenotype group, 16 (21.3%) in hypertrophy phenotype group, and 25 (33.3%) in NCM phenotype group. Significant differences were found among the three groups in age, creatinine, and BNP levels ($p < 0.05$). A total of 51 mutation sites were identified in the 75 patients, of which 50 were point mutations and one was a deletion mutation (c.2563_2565delGAG). Among the 51 point mutations, nine sites were recurrent. The most frequent recurrent mutation was c.2710C > T (6 cases), followed by c.602T > C, c.1357C > T, c.1106G > A, c.2711G > A, c.2513C > T, c.4498C > T, c.5401G > A, and c.848A > T. Sanger validation was performed in 72 cases. Among them, 21 cases (28.0%) had maternal inherited variants, 19 cases (25.3%) had paternal inherited variants, and 32 cases (42.6%) had de novo variants. Mutation sites in

the three phenotype groups were distributed throughout the entire length of the MYH7 gene without significant enrichment in any region. Although mutations in the head region (S1) were more frequent than in the neck region (S2) or tail region (S3), there was no statistically significant difference among the groups ($p = 0.369$). Spearman correlation analysis showed no correlation between genetic functional domain and clinical phenotype, but a correlation was observed between functional domain and prognosis ($p = 0.034$, $r=-0.281$), indicating that mutations in the head region were associated with worse prognosis.

Conclusions

Children with MYH7 gene mutations exhibit diverse clinical phenotypes with no significant enrichment of mutation sites. In this cohort, no correlation was found between functional domain and clinical phenotype, but mutations located in the head region were associated with poorer prognosis. Molecular-level genetic profiling can offer crucial clues for clinical outcome prediction.

Introduction

The structure and sequence of the myosin heavy chain 7 (MYH7) gene were first identified in 1990. It is located on chromosome region 14q11.2 and spans 22,883 bp. The MYH7 gene contains 39 introns and 40 exons, of which 38 exons encode the myosin heavy chain protein. The translation start codon is located at the 9th nucleotide of exon 3, and the protein consists of 1,935 amino acids (Mr 223,111) [1]. Myosin heavy chain protein is expressed in cardiomyocytes and slow-twitch muscle fibers. Myosin is the primary driver of muscle contraction. It interacts with actin and generates mechanical force through ATP hydrolysis, thereby enabling muscle contraction and relaxation.

MYH7 is closely associated with various hereditary cardiac diseases, involving clinical phenotypes such as hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction, arrhythmogenic cardiomyopathy, and distal myopathy, indicating complex clinical manifestations. This study analyzed the clinical characteristics of children with MYH7 gene mutation-associated cardiomyopathy from ten centers in China, aiming to provide a reference for future clinical practice.

Data and Methods

1. General information

This was a retrospective cohort study. Children with MYH7 gene mutations who first visited or revisited Beijing Children's Hospital, Capital Medical University; Beijing Jingdu Children's Hospital; Qingdao Women and Children's Hospital; Children's Hospital of Chongqing Medical University; Beijing Anzhen Hospital, Capital Medical University; Xi'an Children's Hospital; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; Children's Hospital of Soochow University from January 2020 to December 2025 were enrolled. History, clinical manifestations, laboratory results, and echocardiography were recorded for all patients. The data of the children in this study were reported anonymously. This study was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University

(Approval No.: 2026-E-071-R), and informed consent was waived.The flowchart of patient inclusion is shown in Fig. 1.

2.Clinical Data Collection and Grouping

Age, sex, height, weight, underlying diseases, past medical history and other information of the enrolled children were recorded. Based on clinical phenotypes, the patients were divided into the following three groups:

dilation phenotype group: According to the 2019 AHA Classification and Diagnosis of Pediatric Cardiomyopathy[2], in the absence of hemodynamic causes, echocardiography showed increased left ventricular end-diastolic diameter (LVEDD) exceeding the mean LVEDD Z-score > 2 (Z-score calculation website: http://hdb.nbscn.org/zscore), accompanied by systolic dysfunction (left ventricular ejection fraction, LVEF < 40%).

hypertrophy phenotype group: According to the 2019 AHA Classification and Diagnosis of Pediatric Cardiomyopathy[2], in the absence of hemodynamic causes that would explain the observed wall thickness, the maximum diastolic thickness of the interventricular septum (IVS) or left ventricular free wall (LVPW) exceeded the mean left ventricular wall thickness Z-score > 2 (Z-score calculation website: http://zscore.chboston.org).

noncompaction cardiomyopathy(NCM) phenotype group: According to the Jenni echocardiographic diagnostic criteria[3], echocardiography demonstrated abundant trabeculations and intertrabecular recesses, with a ratio of non-compacted to compacted myocardial thickness (NC/C) > 2 at end-systole, leading to a diagnosis of NCM.

3.Pathogenic Gene Testing

Peripheral blood (2 mL each) was collected from the affected children and their family members (parents and other relatives), and genomic DNA was extracted. Targeted capture combined with next-generation sequencing was used to sequence all exons and adjacent intronic regions. The data were aligned to the human reference genome (GRCh37/hg19). The pathogenicity of variants was predicted using bioinformatics software (MutationTaster, PolyPhen-2, SIFT). Suspected pathogenic variants were validated by Sanger sequencing to determine their familial origin. The pathogenicity of novel variants was classified according to the relevant guidelines of the American College of Medical Genetics and Genomics (ACMG).

4. Compound mutation refers to the presence of two or more mutation sites in the MYH7 gene in a child, or the presence of at least one additional gene with a clearly pathogenic mutation (pathogenic/likely pathogenic) besides the MYH7 gene mutation. The scope was defined according to the 2019 AHA Classification and Diagnosis of Pediatric Cardiomyopathy, as detailed in Table 1.

Table 1
Summary of concomitant genes

Group	concomitant genes list
Dilated phenotype group(total: 23)	ACTC1、TNNC1、TNNI3、TNNT2、TPM1、MYBPC3、MYH7、ACTN2、CSRP3、LDB3/ZASP、TCAP、TTN、DSG2、DSP、VCL、DES、EMD、LMNA、SYNE1、SYNE2、SGCD、CRYAB、 RBM20
Hypertrophic phenotype Group(total: 18)	ACTC1、TNNC1、TNNI3、TNNT2、TPM1、MYBPC3、MYH7、MYL2、MYL3、ACTN2、CSRP3、MYOZ2、TCAP、TTN、VCL、DES、LMNA、CAV3、
NCM phenotype Group(total: 8)	ACTC1、TNNT2、TPM1、MYBPC3、MYH7、ACTN2、LDB3/ZASP、TAZ
5.Follow-up indicators and endpoint events	
、In Dilated phenotype group:According to the diagnostic criteria for heart failure with improved ejection fraction in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[4], improvement was defined as LVEF > 40% at follow-up with an absolute increase of ≥ 10% from baseline. No improvement was defined as LVEF < 40% at follow-up or an absolute increase of < 10% from baseline. Endpoint events were defined as death, heart transplantation, or listing for heart transplantation	

、In Hypertrophic phenotype Group: Since interventricular septal/ventricular wall thickening is almost irreversible, endpoint events were defined according to the 2020 AHA/ACC Guideline for the Management of Patients With Hypertrophic Cardiomyopathy[5] as: sudden cardiac death, cardiogenic syncope, surgery/ablation therapy, left ventricular ejection fraction < 50%, or severe ventricular wall thickening (> 30 mm). Follow-up was performed to record the occurrence of endpoint events.

、In NCM phenotype Group: Since there is no internationally unified precise definition of treatment outcomes, based on previous clinical experience, at follow-up, an increase in LVEDD Z-score from baseline accompanied by a decrease in LVEF is defined as progression/worsening; an LVEDD Z-score that is the same as or decreased from baseline accompanied by an increase in LVEF is defined as improvement. Endpoint events were defined as death, heart transplantation, or listing for heart transplantation.

6.Statistical analysis

SPSS 23.0 software (IBM Corp.) was used for data analysis. Normally distributed continuous variables are expressed as the mean ± SD, and the t test was used for comparison between groups. Measurement of data with a nonnormal distribution are represented as median (Q1, Q3), and the Kruskal-Wallis H test was used for comparison between groups, followed comparisons using Dunn's test with Bonferroni correction. Echocardiographic parameters before and after treatment were compared using the Wilcoxon signed-rank test. Categorical variables were expressed as n (%), and comparisons between groups were performed using the chi-square test. Spearman correlation analysis was further conducted. A P-value < 0.05 was considered statistically significant.

Results

1. General clinical data of the children

A total of 75 children, including four families, were enrolled in this study. The median age at first diagnosis of the entire cohort was 20.0 (3.0, 80.0) months, and 47 patients (62.7%) were male. Among them, there were 34 cases (45.3%) in the dilated phenotype group, 16 (21.3%) in the hypertrophic phenotype group, and 25 (33.3%) in the NCM phenotype group. There was a statistically significant difference in age of onset among the three groups ($p < 0.05$), while no statistically significant difference was observed in sex distribution. Details are shown in Table 2.

Table 2
the characteristics of patients

	Group			***H^2 /χ^2 value (n = 2)***	***p-value***
	Dilated phenotype group (n = 34)	**Hypertrophic phenotype Group (n = 16)**	**NCM phenotype Group (n = 25)**		
Clinical Characteristics					
Sex male/female	20/14	9/7	18/7	-	-
Age(month,M(p25,p75))	5.0(2.0,18.5)	96.0(63.7,140.0)	33.0(5.0,79.0)	21.506	0.000*
family history +/-	11/23	2/14	6/19	-	-
Cardiac medication, n (%)					
Use of cardiotonic drug	34(100%)	0	25(100%)	-	-
Use of ACEI	34(100%)	0	25(100%)	-	-
Use of beta-blocker	15(44.1%)	16(100%)	4(16.0%)	-	-
Use of diuretic agents	34(100%)	0	20(80%)	-	-
Use of gulcocorticoids	18(52.9%)	0	0	-	-
Use of IVIG	26(76.5%)	0	18(72.0%)	-	-

2. Test results of children

Comparisons among the three groups showed statistically significant differences in creatinine and brain natriuretic peptide(BNP)($p < 0.05$), while no statistically significant differences were found in Aspartate Transaminase(AST), Alanine Transaminase(ALT), creatine kinase(CK),creatine kinase-MB(CK-MB), or cardiac troponin($p > 0.05$), as shown in Table 3

Table 3
main results of patients

	Group			H^2 value (n = 2)	p-value
	Dilated phenotype group (n = 34)	Hypertrophic phenotype group (n = 16)	NCM phenotype Group (n = 25)		
Laboratory results,median(p25,p75)					
BNP(ng/ml)	34.1(10,90.62)	592.0(50.5,1240.0)	32.0(15.3,228.9)	7.627	0.022*
hs-TnI(pg/ml)	0.032(0.011,1.514)	0.035(0.006,0.395)	0.007(0.001,0.252)	5.567	0.062
CK-MB(ng/ml)	3.5(2.1,11.1)	4.7(1.7,6.8)	4.5(2.1,7.8)	0.023	0.989
CK(U/L)	97.0(62.0,128.0)	103.0(87.7,126.0)	117.0(75.5,161.3)	2.73	0.255
creatinine(ng/ml)	26.5(19.2,30.0)	44.4(31.7,36.4)	31.8(22.2,38.0)	14.88	0.001*
Uric Acid(umol/l)	286.8(231.6,358.8)	338.1(266.4,442.2)	239.1(194.2,339.2)	5.936	0.051
AST(U/L)	37.2(29.0,45.3)	32.2(24.1,38.0)	36.0(26.5,42.9)	3.572	0.168
ALT(U/L)	19.2(13.0,25.2)	15.0(9.0,22.7)	18.9(12.5,26.5)	1.793	0.408
Echocardiogram-first,median(p25,p75)					
LVEDD-z value	5.5(3.9,7.3)	0.1(-0.4,0.93)	1.74(1.14,2.98)	42.42	0.000*
LVEF(%)	36.0(27.8,45.0)	67.0(64.0,73.0)	50.0(46.0,54.0)	57.89	0.000*
IVS(mm)	4.2(3.8,5)	7.0(5.1,9.3)	4.5(3.7,4.9)	14.26	0.001*
LVPW(mm)	4(3.4,4.7)	11.2(8.8,20.7)	4.0(3.8,4.7)	9.67	0.013*
NC/C	-	-	3.4(2.7,3.9)	-	-
Echocardiogram-following(till 2025-12-31),median(p25,p75)					
LVEDD-z value	2.9(2.1,4.2)	0.3(-1.3,1.4)	2.2(0.8,3.3)	4.355	0.113
LVEF(%)	51.0(42.9,61.7)	69.0(62.5,74.8)	62.0(57.8,63.0)	2.667	0.264
IVS(mm)	5.0(5.0,6.0)	9.15(5.3,10.2)	5.7(4.0,6.4)	8.372	0.015*
LVPW(mm)	5.0(4.6,5.3)	13.6(9.6,20.7)	5.9(4.1,6.9)	4.796	0.047*

3. Echocardiogram results

Among the three groups, there were statistically significant differences in LVEDD-Z score, LVEF, IVS, and LVPW at the initial echocardiogram ($p < 0.05$). Pairwise comparisons showed statistically significant differences between the dilated phenotype group and the hypertrophic phenotype group, between the

hypertrophic phenotype group and the NCM group, and between the dilated phenotype group and the NCM group ($p < 0.001$, $p < 0.001$, $p = 0.045$). Using the Wilcoxon signed-rank test, changes in LVEDD-Z score before and after treatment in the dilated phenotype group were statistically significant ($Z = -2.904$, $P = 0.004$), and changes in LVEF were also statistically significant ($Z = 2.423$, $P = 0.015$). After treatment and follow-up until December 2025, children in the ventricular dilation phenotype group showed a significant reduction in LVEDD and improvement in LVEF. Children in the left ventricular non-compaction phenotype group showed no significant improvement in LVEDD but improvement in LVEF. As a result, differences in LVEDD and LVEF among the three groups were no longer statistically significant. However, because IVS thickness and LVPW thickness further increased in the hypertrophic phenotype group, differences in IVS and LVPW among the three groups remained statistically significant.

4. MYH7 gene variant spectrum analysis

A total of 51 mutation sites were identified in the 75 children, including 50 point mutations and 1 deletion mutation (c.2563_2565delGAG). Among the 51 point mutations, 9 sites were recurrent. The most frequent recurrent mutation was c.2710C > T (6 cases), followed by c.602T > C, c.1357C > T, c.1106G > A, c.2711G > A, c.2513C > T, c.4498C > T, c.5401G > A, and c.848A > T. Sanger validation was performed in 72 cases. Among them, 21 cases (28.0%) had maternal inherited variants, 19 cases (25.3%) had paternal inherited variants, 32 cases (42.6%) had de novo variants, and 3 cases (4.0%) were not validated. The pathogenicity classification was pathogenic in 38 children and likely pathogenic in 37 children.

Among the 75 children, 5 patients carried compound mutations in the MYH7 gene, including 4 with exonic mutations and 1 with an intronic mutation. The additional mutations in these cases were all classified as variants of uncertain significance (VUS). Regarding concomitant gene variants, 35 patients harbored additional gene mutations of uncertain significance. Among these, TTN mutations were identified in 18 cases, MYBPC3 mutations in 4 cases, FLNC mutations in 3 cases, CACNA1C mutations in 2 cases, and NEXN mutations in 2 cases.

5. Concomitant gene variant spectrum analysis

Three children (4.0%) had concomitant mutations in other genes, all of which were suspected pathogenic mutations: TNNI3 (c.235C > T), TTN (c.10819G > T), and RBM20 (c.1172T > A). In addition, 24 children carried concomitant gene mutations with a pathogenicity classification of variant of uncertain significance. The child with the deletion mutation also carried one point mutation of uncertain significance (c.4384G > A).

6. Follow-up outcomes

After an average follow-up of 65.1 ± 43.9 months (until December 2025), 23 children (67.6% of the group) in the dilated phenotype had their LVEF recovered to the normal range, while 11 had not yet recovered. Two children in the dilated phenotype experienced endpoint events: one died of heart failure 15 months after

disease onset despite resuscitation efforts, and one underwent heart transplantation 84 months after disease onset. In the ventricular hypertrophy group, one child experienced an endpoint event (underwent modified Morrow surgery 58 months after initial diagnosis) and is currently alive. All children in the left ventricular non-compaction phenotype group improved after treatment, with LVEF > 50% at an average follow-up of 63.9 ± 41.1 months (until December 2025), and no endpoint events occurred.

7. Genotype–phenotype association analysis

Mutation sites of the MYH7 gene in the three clinical phenotypes were distributed throughout the entire length of the gene without significant enrichment in any region. Although mutations in the head region (S1) were more frequent than in the neck region (S2) or tail region (S3), there was no statistically significant difference among the groups (p = 0.369), as shown in Table 4, Fig. 2and Fig. 3. Mutations in children with the ventricular dilation phenotype were scattered throughout the entire gene without significant clustering. In the ventricular hypertrophy and non-compaction groups, mutations mostly occurred in the head and neck regions. Spearman correlation analysis was performed to assess the relationship between functional domain and clinical phenotype (p = 0.81), indicating no correlation between functional domain and clinical phenotype. Regarding prognosis, Spearman correlation analysis examined the correlation between functional domain and prognosis, and we found a significant negative correlation (p = 0.034, r=-0.281), meaning that mutations in the head region were associated with worse prognosis.

Table 4

	Group			*p-value*
	Dilated phenotype group (n = 34)	Hypertrophic phenotype group (n = 16)	NCM phenotype Group (n = 25)	
mutation located in the S1 region, n(%)	20(58.8)	12(75.0)	14(56.0)	0.81
mutation located in the S2 region, n(%)	7(20.6)	4(25.0)	8(32.0)	
mutation located in the S3 region, n(%)	7(20.6)	0	3(12.0)	

Discussion

MYH7 is the most common pathogenic gene in hereditary cardiomyopathies in children[5]. According to the 2019 AHA Classification and Diagnosis of Pediatric Cardiomyopathy, MYH7-related pediatric cardiomyopathy phenotypes include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and noncompaction cardiomyopathy (NCM). However, no children with the RCM phenotype were identified in our study cohort. In our cohort, all mutations were classified as

pathogenic or likely pathogenic. By family Sanger validation, 44.4% of the children carried de novo mutations, and 55.6% inherited the mutation from their father or mother. Of particular note, our cohort included four families with mutation sites c.602T > C, c.2710C > T, c.2711G > A, and c.5401G > A, respectively. In these four families, both affected children exhibited varying degrees of left ventricular non-compaction and cardiac dysfunction. MYH7 follows an autosomal dominant inheritance pattern. We propose that this phenotypic variability (same gene mutation, same parents, but different disease severity) is most likely due to differences in penetrance, possibly because mutations in other genes enhance or attenuate the pathogenic effect of the main gene (MYH7). In three of these four families, the child with worse cardiac function carried an additional VUS (in TTN, FLNC), as detailed in Table 5.

Table 5

Patients	MYH7 mutation site	Origin of mutation	LVEF(%)	Names of concomitant genes	concomitant genes mutation site	Origin of concomitant genesmutation
A	c.602T > C	paternal inherited	60	-		
B	c.602T > C	paternal inherited	39	-		
C	c.2710C > T	paternal inherited	69	-		
D	c.2710C > T	paternal inherited	41	FLNC	c.1310G > T	Father
E	c.2711G > A	paternal inherited	56	-		
F	c.2711G > A	paternal inherited	28.9	TTN	c.96758T > C	maternal inherited
G	c.5401G > A	maternal inherited	61	-		
H	c.5401G > A	maternal inherited	39	TTN	c.10819G > T	maternal inherited

In this study, three children experienced endpoint events. Two were in the dilated phenotype (one died of heart failure, one underwent heart transplantation), with mutation sites c.2710C > T (neck region) and c.1573G > A (head region), respectively. One child in the ventricular hypertrophy group (survived sudden cardiac arrest and subsequently underwent modified Morrow surgery) carried mutation c.2156G > A (head region). The child in the dilated phenotype who received heart transplantation belonged to family D mentioned above. This further suggests that although this site is located in the neck region, it still has great potential to become a hot spot, and deserves focused attention in our future studies.

Myosins are actin-based motor molecules with ATPase activity essential for muscle contraction. Forms regular bipolar thick filaments that, together with actin thin filaments, constitute the fundamental

contractile unit of skeletal and cardiac muscle[6–9].The head region of the MYH7 gene is central to cardiac force generation, and its function depends on the coordinated action of two core subdomains:

 ATP-binding site: Encoded by amino acids from exons 4-6, this site is responsible for ATP binding and hydrolysis. The energy released from ATP hydrolysis drives conformational changes in the myosin head, enabling the cross-bridge cycling with actin, which serves as the energy source for force generation.

 Actin-binding site: Comprising a “pre-binding site” (encoded by exons 7-9) and a “post-binding site” (encoded by exons 14-16), this site binds to actin (the core component of thin filaments) through hydrophobic interactions and hydrogen bonds, forming the actin-myosin complex. It is a critical interface for force transmission. Notably, recent hot-spot mutations such as R453W and E525K are located in this region.

The neck region of the MYH7 gene is encoded by exons 20-21 and serves as the binding site for myosin light chains. The structural integrity of this region directly affects the efficiency of contractile force transmission. Mutations in this region do not directly affect ATP hydrolysis or actin binding but can lead to abnormal contractile coordination. If light-chain binding is impaired, the efficiency of force transmission may decrease, resulting in a dilated cardiomyopathy (DCM) phenotype; if light-chain binding is enhanced, it may indirectly increase the contractile activity of the head, leading to a hypertrophic cardiomyopathy (HCM) or mixed phenotype.

The tail region of the MYH7 gene is responsible for thick filament assembly and structural stability. Mutations in this region predominantly impair myofilament structural integrity rather than directly compromising contractile force production, and are thus closely linked to phenotypes including DCM and NVM. The pertinent data are summarized in Table 6.

In our cohort, all MYH7 mutations in the ventricular hypertrophy group were located in the head or neck regions, while some mutations in the dilated phenotype and the left ventricular non-compaction group were located in the tail region, which is largely consistent with the functional domains described. The clinical phenotypes in this group of patients were diverse, with no significant clustering of mutations in any particular region. There was no correlation between gene functional domain and clinical phenotype. However, mutations in the head region were associated with a worse prognosis, a finding that is consistent with reports in the literature.

Table 6

Functional domain	Subdomain	Exon range
Head region	ATP-binding site, actin-binding site, switch region (Switch I/II)	Exons 1–19
Neck region	IQ motif, light chain binding domain	Exons 20–22
Tail region	Coiled-coil domain, tail–tail interaction domain, C-terminal regulatory domain	Exons 23–40

Previous studies have directly compared the distinct molecular effects of different mutations at the same position (Q222) of the MYH7 gene. It was reported that the HCM-associated mutation (Q222K) increases ATPase activity and ATP-binding kinetics, whereas the DCM-associated mutation (Q222H) produces opposite effects. In vitro motility assays demonstrated that Q222K enhanced actin sliding velocity by 32%, while Q222H reduced it by 43%[10]. Notably, in our own cohort, we also observed different mutations (Y283C vs. Y283F) at the same genetic locus, which gave rise to distinct clinical phenotypes and varying disease severities. The patient carrying the Y283C mutation presented with noncompaction of ventricular myocardium, with an initial LVEDD-z of 2.87 and LVEF of 45%; in contrast, the two patients with the Y283F mutation exhibited ventricular dilation, with initial LVEDD-z values of 7.96 and 5.36, and LVEF of 27% and 36%, respectively. Of particular interest, both Y283C and Y283F are neutral-charge substitutions that do not involve changes in net charge. In Y283C, the two amino acids share largely similar polarity; however, in Y283F, phenylalanine lacks a hydroxyl group (–OH) compared with tyrosine, which may alter the polarity and hydrogen-bonding capacity at this site, thereby potentially affecting protein microstructure and function. Furthermore, according to the ClinVar database, another mutation, p.Tyr283Asp (Y283D), which replaces the neutral tyrosine with negatively charged aspartic acid, is also classified as "likely pathogenic." These observations suggest that in gene-based precise subtyping, greater attention should be paid to dynamic changes at the molecular level, rather than focusing solely on domain-based analyses.

Furthermore, in our literature review, we identified a previous study on pediatric MYH7-associated dilated cardiomyopathy that included 44 patients (from 33 independent families) across 13 centers[1]. After a median follow-up of 6.1 years, 36% of the patients had reached the endpoint of end-stage heart failure (14 transplantation, 1 death), and only 29% exhibited left ventricular reverse remodeling (LVRR). The prognosis of the enrolled children in our study was significantly better than that reported in the literature. We speculate that this difference may be related to the treatment with intravenous immunoglobulin (IVIG). IVIG has a dual effect of immune replacement and immune modulation: as a biological preparation rich in broad-spectrum IgG antibodies, it can enhance humoral immunity through immune protection barriers; at the same time, it interacts with immune cells such as macrophages, regulates the release of inflammatory cytokines, and neutralizes microbial antigens, superantigens, and autoantibodies, blocking Fc receptors[11–12]. The net effect is downregulation of pro-inflammatory mediators and upregulation of anti-inflammatory mediators, tilting the body's inflammatory/anti-inflammatory balance toward an anti-inflammatory net effect. Studies have shown that IVIG-induced changes in the inflammatory/anti-inflammatory balance are significantly correlated with improvements in left ventricular ejection fraction (LVEF)[13–14]. Based on these effects, IVIG has gradually been applied in the treatment of cardiomyopathies in recent years. In this study, left ventricular function in children treated with IVIG improved significantly compared with the control group, further confirming that IVIG may improve cardiomyocyte remodeling and cardiac function by modulating the immuno-inflammatory network.

Limitations

Finally, our study has several limitations. First, as a retrospective longitudinal cohort study, the study spanned a relatively long period. Although we re-evaluated the pathogenicity of genetic variants according

to the latest guidelines, the genetic testing of some early-enrolled children may have been limited by insufficient sequencing depth due to the testing technologies available at different times. Second, only 75 children were ultimately enrolled in this study. Although this sample size represents the largest cohort reported to date in the field of monogenic pediatric cardiomyopathy, the relatively small absolute sample size may still limit statistical power and subgroup analyses. In the future, larger-scale, prospective studies with longer follow-up durations are needed to further validate the findings of this study and to deepen our understanding of the disease spectrum.

Conclusions

Children with MYH7 gene mutations exhibit diverse clinical phenotypes with no significant enrichment of mutation sites. In this cohort, no correlation was found between functional domain and clinical phenotype, but mutations located in the head region were associated with poorer prognosis. Molecular-level genetic profiling can offer crucial clues for clinical outcome prediction.

Abbreviations

MYH7
myosin heavy chain 7
DCM
dilated cardiomyopathy
HCM
hypertrophic cardiomyopathy
NCM
noncompaction cardiomyopathy
LVEF
left ventricular ejection fraction
LVEDD
left ventricular end-diastolic diameter
BNP
brain natriuretic peptide
IVIG
intravenous immunoglobulin
VUS
variant of uncertain significance
ACMG
American College of Medical Genetics and Genomics
AHA
American Heart Association

Declarations

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University (Approval No.: 2026-E-071-R). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was waived by the ethics committee.

Consent for publication

Not applicable.

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Author Contribution

Prof. YY.X. and Prof. L.H. provided conceptualization, methodology, and supervision. YYf conducted the investigation, data curation, and wrote the original draft. All authors reviewed and edited the manuscript and approved the final version.

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Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

References

1. de Frutos F, et al. Clinical Features and Outcomes of Pediatric MYH7-Related Dilated Cardiomyopathy. J Am Heart Assoc. 2024;13(21):e036208.
2. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in Children: Classification and Diagnosis: A Scientific Statement From the American. Heart Association Circulation. 2019;140(1):e9–68.
3. Jenni R, Oechslin E, Schneider J, et al. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart. 2001;86(6):666–71.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263–421.
5. Ware SM, et al. Age and Sex Differences in the Genetics of Cardiomyopathy. J Cardiovasc Transl Res. 2023;16:1287–302.
6. Rassier DE. Mechanisms of myosin II force generation: insights from novel experimental techniques and approaches. Physiol Rev. 2025;105(1):1–93.
7. Irving M. Functional control of myosin motors in the cardiac cycle. Nat Reviews Cardiol. 2024;21(9):653–69.
8. Sweeney HL, Houdusse A. Myosin Structures. Adv Exp Med Biol. 2020;1239:7–19.
9. Sweeney HL, Houdusse A. How Myosin Generates Force on Actin Filaments. Trends Biochem Sci. 2016;41(12):989–97.
10. Kawana M, Reddy Goluguri R, Dawood A, Spudich JA, Ruppel K. Molecular characterization of a novel MYH7 mutation Q222H in a patient with severe dilated cardiomyopathy. Biophys J. 2023;122(3S1):258a.
11. Aukrust P, Yndestad A, Ueland T, Damås JK, Frøland SS, Gullestad L. The role of intravenous immunoglobulin in the treatment of chronic heart failure. Int J Cardiol. 2006;112(1):40–5.
12. Nussinovitch U, Shoenfeld Y. Intravenous immunoglobulin - indications and mechanisms in cardiovascular diseases. Autoimmun Rev. 2008;7(6):445–52.
13. Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation. 2001;103(2):220–5.
14. Prasad AN, Chaudhary S. Intravenous immunoglobulin in children with acute myocarditis and/or early dilated cardiomyopathy. Indian Pediatr. 2014;51(7):583–4.

Figures

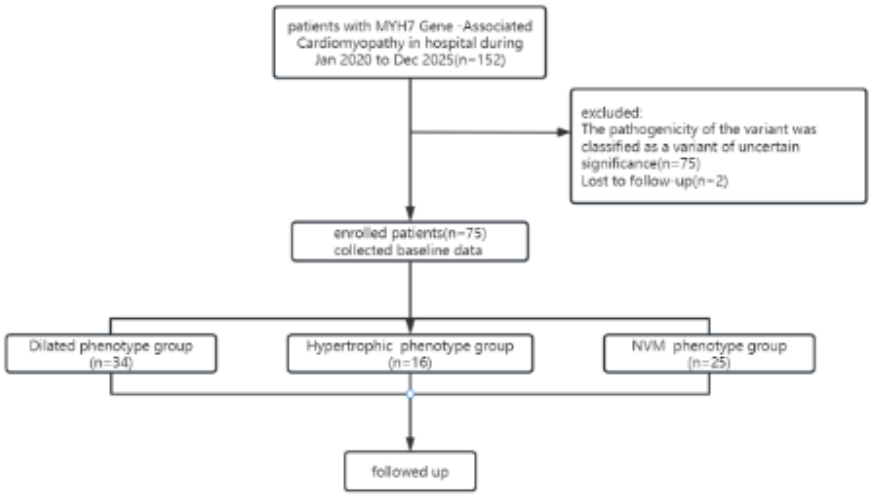


Figure 1

flow chart

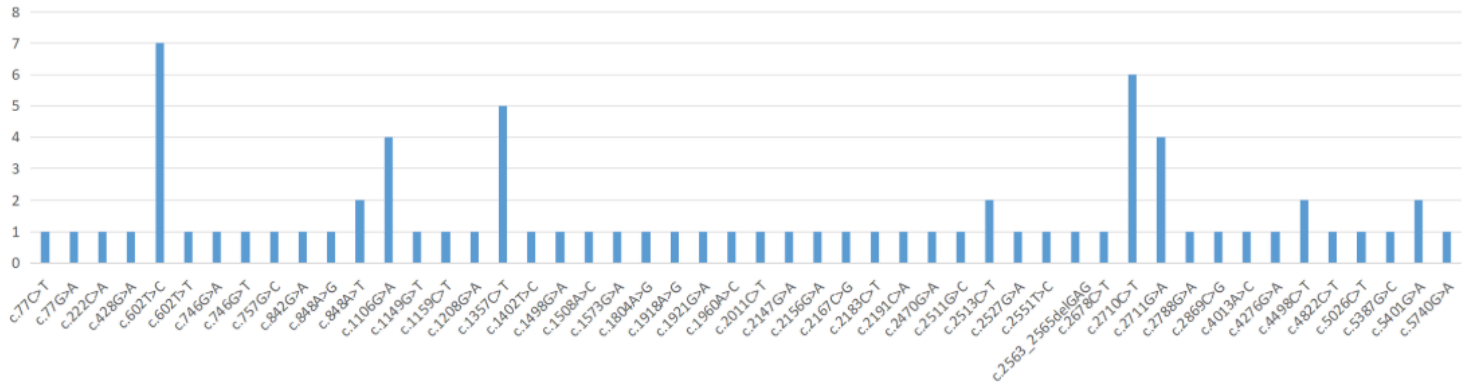


Figure 2

Frequency distribution of MYH7 gene mutation sites among the study cohort.

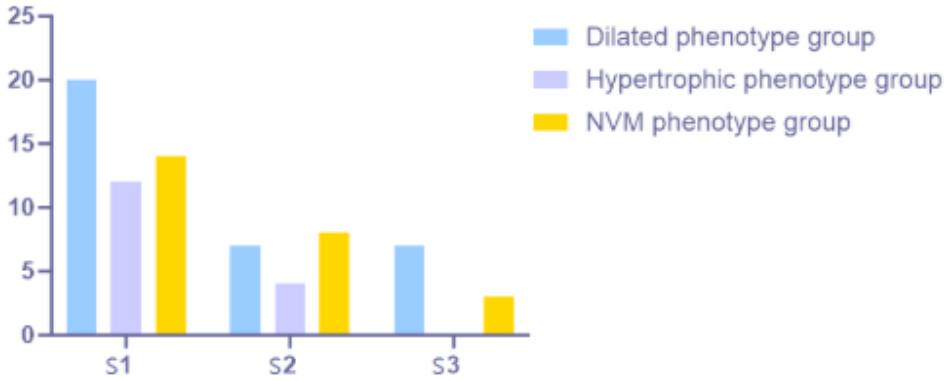


Figure 3

Bar chart showing distribution of clinical phenotypes and functional domains